Inhibition of CXCR4-Mediated Prostate Bone Metastasis by the TumorSuppressor PTEN

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**Prostate Cancer**

- It is the most diagnosed cancer in males.
- It is the second leading cause of death out of all cancers in males.

### Estimated New Cases*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>192,280</td>
<td>25%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,090</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,590</td>
<td>10%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>52,810</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>39,080</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,990</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,430</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,630</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,240</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,050</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>766,130</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>88,900</td>
<td>30%</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,360</td>
<td>9%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,240</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,030</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,590</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,090</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,490</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,180</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,830</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,160</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>292,540</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Metastasis

Primary tumour

- CXCR4
- PAR1
- CXCR2
- EP2

Stroma

- NFkB
- COX2
- PGE2
- HIF1α
- SDF1

ECM degradation

- Tumour cell
- IL8
- PGE2

Growth and survival

- COX2
- NFkB

Intravasation

- Thrombin
- MMP2
- MMP9

Tumour escape

- Migration

Circulation

- VEGF
- Extravasation

Metastasis

- SDSF1
- Lung
- Liver
- Bone
- Lymph node

Nature Reviews Cancer
Once in the bone, tumors are incurable to therapy, and contribute to increased mortality through unknown mechanisms.

The tumor and bone interact in a vicious cycle, where tumor-secreted factors stimulate bone cells, which in turn release growth factors and cytokines that act on tumor cells to further influence metastasis.
Member of the chemokine receptor family
It is a G-protein coupled receptor
It is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1α)
Activation of chemokine receptors results in a diverse array of biological functions such as metastasis
In our prostate cancer model system, CXCR4 is overexpressed on the cell surface, which directs metastatic cells to tissues, where its ligand is overexpressed.
CXCR4-mediated metastasis

1. Cancer cells detach and migrate to blood vessel
2. Cancer cells migrate to tissue with a high SDF-1 concentration
3. Cancer cells accumulate and form new tumour
Phosphate and tensin homolog deleted on chromosome 10 (PTEN)

- Prostate cancer cells have been shown to exhibit a loss of the tumor suppressor PTEN, which also correlates with increased malignancy.
- Second most mutated tumor suppressor in most human cancers
- Functions as a tumor suppressor
- Inactivation of PTEN is associated with a variety of cancers including prostate cancer.
- Targets PI3K pathway
Results
FIGURE (A): Western Blot analysis of the total cellular proteins from 293T, Du145, C42, LnCaP & PC3 cells using antibodies specific to P-TEN & ERK ½ (Control).

FIGURE (B): RT-PCR analysis of total cellular mRNA from 293T, Du145, C42, LnCaP & PC3 cells using PTEN and L-19 primers.
Expression of CXCR4 by Flow Cytometry:

(A) LnCaP cells and (B) PC3 cells express CXCR4. (B) Cell surface expression of chemokine receptor CXCR4 was measured by flow cytometry. Cells were stained with anti-CXCR4 (black line) or secondary antibody alone as a negative control (red line).
PTEN inhibit CXCR4-mediated migration through human bone marrow endothelial cells in a transendothelial migration assay.
DISCUSSION

The data show that:
- PTEN was not expressed in PC3, C42, & LnCaP at protein level.
- Expression of PTEN at the mRNA level was detected in LnCaP & C42 but not in PC3.
- PTEN was expressed in Du145 at both protein and mRNA level.
- CXCR4 surface expression was detected in PC3 and LnCaP cells.
- PTEN inhibited CXCR4-mediated transendothelial migration through human bone marrow endothelial cells.
FUTURE DIRECTIONS:

To determine whether PTEN inhibits CXCR4-mediated metastasis to distant organs

• Repeat transendothelial assay through bone marrow endothelial cells

To investigate which signaling pathway is involve in CXCR4-mediated transendothelial migration

• Western blot
Acknowledgement:

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CCRTD
THE END
Thank You!